The reaction of β-nitrostyrenes with 2-methoxyfuran: a novel formation of isoxazoline *N*-oxide together with Michael adducts

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2-Methoxyfuran reacts with β-nitrostyrenes to give Michael adducts. Interestingly, isoxazoline *N*-oxides were obtained in the reactions with β-nitrostyrenes possessing additional electron-withdrawing groups (COPh and CO_2Et).

We have been studying the Diels–Alder reactions of furan derivatives with some electron deficient dienophiles[1] for some time. Furans are known to be rather unreactive dienes because of their stabilized 6π-aromatic electronic configuration and the easy occurrence of the retro-Diels–Alder reaction.[2] Hence reactions of furans require stronger dienophiles to make them proceed. In some instances, Lewis acids[3a,c–e] and/or high pressure[3b–e] were employed in the reactions with less-reactive dienophiles. We had employed methyl 3-nitroacrylate in the reactions with furans and observed that the reactions gave the expected Diels–Alder adducts in satisfactory yields.[1a]

Nitro-substituted olefins are powerful and versatile reagents[4] and they show high potential in Michael, Diels–Alder and 1,3-dipolar cycloaddition reactions.[5] In this report, we describe some interesting new reactions of β-nitrostyrenes with electron-rich furans (Scheme 1).

No reaction of nitrostyrenes with furan or 2-methylfuran took place, therefore in the present study we used 2-methoxyfuran as a more reactive diene. A typical experimental procedure was as follows: to a stirred solution of 2-methoxyfuran (**1**, 1.5 mmol) in dichloromethane (3 ml) was added β-bromo-β-nitrostyrene (**2d**, 1.1 mmol) at room temperature under a nitrogen atmosphere. After stirring for 3 days, the resultant mixture was evaporated under reduced pressure to give an oil, which was separated by column chromatography on silica gel (elution solvent: ethyl acetate–hexane, 1 : 9) to give a mixture of Michael adducts (**3d**, 34%

yield, run 4 in Table 1). An NMR analysis showed that the mixture was composed of a 1 : 1 mixture of two diastereo-isomers (**3**, **3′**), which showed different signals for the furanyl and alkyl protons [**3**: δ 6.40 (d, *J* = 10.7 Hz), 6.20 (d, *J* = 3.3 Hz), 5.07 (d, *J* = 3.3 Hz), 4.66 (d, *J* = 10.7 Hz); **3′**: 6.36 (d, *J* = 10.7 Hz), 6.06 (d, *J* = 3.3 Hz), 5.00 (d, *J* = 3.3 Hz), 4.71 (d, *J* = 10.7 Hz)].

Results of reactions with other β-nitrostyrenes are given in Table 1. In general, β-nitrostyrenes (**2a–d**) reacted with 2-methoxyfuran to give the corresponding Michael adducts (Table 1, runs 1–4). However, the β-methyl-β-nitrostyrene (**2e**, run 5) gave no adduct even after 4 days, because of the presence of the electron-donating methyl group at the β-position. Hence, we expected that a more electron-deficient β-nitrostyrene derivative could give Diels–Alder adducts in reactions with 2-methoxyfuran. Accordingly, the reaction of *E*-β-benzoyl-β-nitrostyrene (**2f**) with 2-methoxyfuran was exam-

Table 1 Reactions of β-nitrosyrenes with 2-methoxyfuran

Run	Nitrostyrene	Product[a]	
		Michael adduct and yield (%)	Isoxazoline and yield (%)
1	**2a**	**3a** (23)	
2	**2b**	**3b** (31)	
3	**2c**	**3c** (36)	
4	**2d**	**3d** (34)	
5	**2e**	**3e** (0)	
6	**2f**	**3f** (trace)	**4f** (27)
7	**2g**	**3g** (13)	**4g** (64)

[a] All compounds gave satisfactory spectroscopic analysis data.
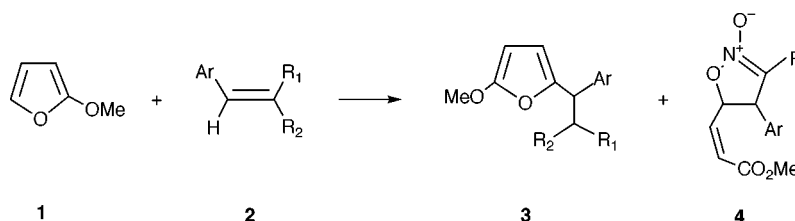
	Ar	R_1	R_2		R
2a, 3a	Ph	H	NO_2		
2b, 3b	*p*-MeOPh	H	NO_2		
2c, 3c	*p*-ClPh	H	NO_2		
2d, 3d	Ph	Br	NO_2		
2e, 3e	Ph	Me	NO_2		
2f, 3f	Ph	COPh	NO_2	**4f**	COPh
2g, 3g	Ph	NO_2	CO_2Et	**4g**	CO_2Et

Scheme 1 Reaction of β-nitrostyrenes (**2**) with 2-methoxyfuran (**1**).

ined in the hope that the Diels–Alder reaction would occur. Surprisingly, the reaction gave neither Michael nor Diels–Alder adducts. Instead, an unexpected product (**4f**, 27% yield, run 6) was obtained, which showed no evidence of furanyl ring signals in its ¹H- and ¹³C-NMR spectra.[6] The structure of **4f** was finally determined to be an isoxazoline *N*-oxide derivative by single crystal X-ray diffraction[7] (Fig. 1). **4f** shows a *cis* conformation between the phenyl and vinyl groups. Similar stereoselectivity was also observed in the product of the reaction of *Z*-β-ethoxycarbonyl-β-nitrostyrene (**2g**) with 2-methoxyfuran to form the *trans*-isoxazoline *N*-oxide derivative (**4g**, 64% yield, run 7). Furthermore, a Michael adduct in lower yield (**3g**, 13%) was also observed in this reaction. These results are informative and imply that the product formation process involves a sterically controlled inter- or intramolecular reaction.

Two processes (Schemes 2 and 3) may account for the formation of the isoxazoline *N*-oxide ring. In Scheme 2, the mesomeric form of 2-methoxyfuran (**1′**) adds to the polarized β-nitrostyrene derivative (**2g′**) to give the adduct **A**. This inter-
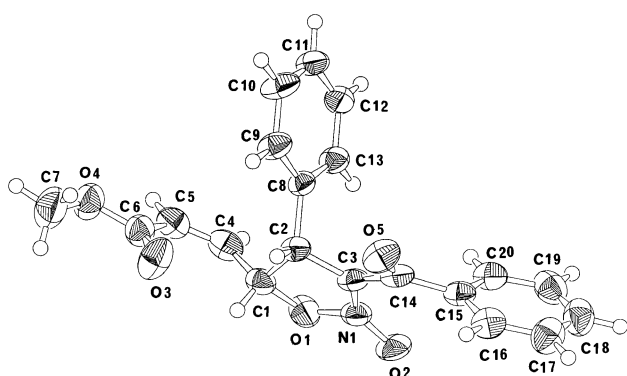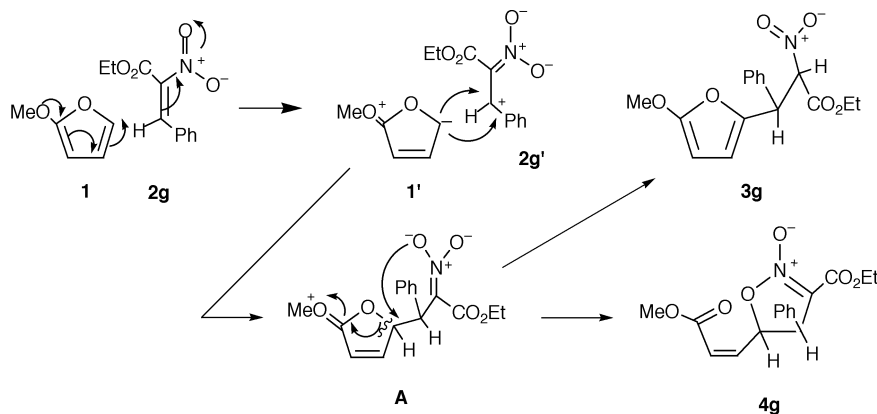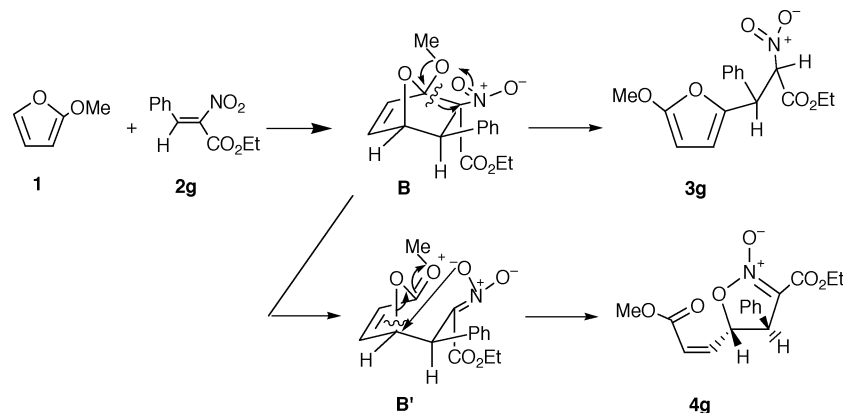
mediate may be transformed into the Michael adduct (**3g**) by ordinary electron and proton transfer, or it could undergo ring formation to give an isoxazoline *N*-oxide (**4g**) as depicted in Scheme 2. An interesting mechanistic feature is that the carbon–oxygen bond fission of the furan ring is induced by an intramolecular nucleophilic attack by the nitronate anion to generate the isoxazoline *N*-oxide ring.

In an alternate route (Scheme 3), cycloaddition of the furan (**1**) and the β-nitrostyrene (**2g**) yields the Diels–Alder adduct **B**.[8] This adduct may be transformed into the Michael adduct (**3g**) by cleavage of the cyclohexenyl ring, attributable to the steric interaction between the phenyl group and the nitro group. On the other hand, cleavage of the cyclohexenyl ring, attributable to the mesomeric form of the methoxy group and the steric effect, followed by intramolecular attack of the nitronate anion and cleavage of the oxygen bridge results in formation of the isoxazoline *N*-oxide ring.

The former route (Scheme 2) is not favored as a stereochemical explanation because of conformational retention difficulties in the intermediate **A**. Also, attack on both faces of the styrene (**2g′**) by the furan (**1′**) should lead to the formation of two **A** adducts; both *cis* and *trans* products should be produced by this mechanism. However, in the latter interconversion (Scheme 3), the nitronate ion attacks the allylic carbon, accompanying the conformation retention of the *exo*-allylic hydrogen and the benzyl carbon. Thus, the intramolecular nucleophilic substitution proceeds by an S$_N$i-like mechanism and this, under stereocontrol, gives rise to a *trans* configuration at the position between the hydrogens. Also, in the reaction of the β-nitrostyrene **2f** with the furan **1**, the position between the hydrogens adopts a *cis* configuration in a similar route as that above. Interestingly, the isoxazoline *N*-oxide was not formed *via* the Michael intermediate, as no trace of the isoxazoline *N*-oxide was detected after allowing the authentic Michael adduct to stand in chloroform at room temperature for two weeks.

Fig. 1 The structure (ORTEP) of an isoxazoline *N*-oxide (**4f**).

Scheme 2

Scheme 3

Further investigation of these rearrangements and their future possible applications are currently in progress in our laboratory.

Acknowledgements

Notes and references

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6 In particular, the ^{1}H-NMR spectrum of **4f** was characterized by a double doublet at 5.75 ($J = 1.5$, 11.6 Hz) and 6.48 ($J = 7.5$, 11.6 Hz) ppm for the unsaturated CH group, while the ^{13}C-NMR signals arising from two carbonyl groups appeared at 165.7 and 184.9 ppm. The IR spectra showed the presence of C=N and C=N–O groups at 1450 and 1410 cm^{-1}, and the absence of an NO_2 group (1570 and 1354 cm^{-1}). Other NMR spectral data: ^{1}H-NMR: 3.61 (s, 3H), 5.26 (d, $J = 4.1$ Hz, 1H), 5.91 (dd, $J = 4.1$, 7.5 Hz, 1H), 7.18, 7.27, 7.42, 7.52, 7.72; ^{13}C-NMR: 52.0, 53.4, 118.8, 123.1, 128.4, 128.5, 128.9, 129.1, 133.4, 141.6 ppm.

7 X-Ray crystallographic analysis was carried out on a Rigaku AFC5R diffractometer. The diffraction date were collected with MoKα radiation and 4350 independent reflections were used to solve the structure by the teXsan program. All non-H atoms were located by direct methods using SIR92 and refined anisotropically. Crystal data for $C_{20}H_{17}NO_5$: formula weight 339.35, monoclinic space group $P2_1/c$, $a = 15.197(1)$, $b = 5.808(2)$, $c = 19.563(1)$ Å, $\beta = 95.321(5)$, $U = 1719.2(6)$ Å^3, $Z = 4$, $d_{calc} = 1.31$ g cm^{-1}, $R = 0.055$ ($R_w = 0.045$) for 4509 reflection data with $I > \sigma$ and 2823 variables.
CCDC reference number 440/175. See http://www.rsc.org/suppdata/nj/b0/b001049i/ for crystallographic files in .cif format.

8 Ranganathan *et al.* reported that furan and nitroethylene gave 2-(β-nitromethyl)furan and proposed that the Michael product was produced from a Diels–Alder adduct: D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra and R. Iyengar, *J. Org. Chem.*, 1980, **45**, 1185. The regioselectivity for the Diels–Alder reaction might be predicted by the calculated coefficients[9] of the olefinic carbon atoms and the nitrogen atoms. However, stereoselectivity was unexpected from the secondary orbital interaction but predicted by means of the AM1 transition state model using the Spartan v. 5.0.1 package (ΔH (the heat of formation) *exo*-nitro compound: -44.8 kcal mol^{-1}, *endo*-nitro compound: -41.5 kcal mol^{-1}).

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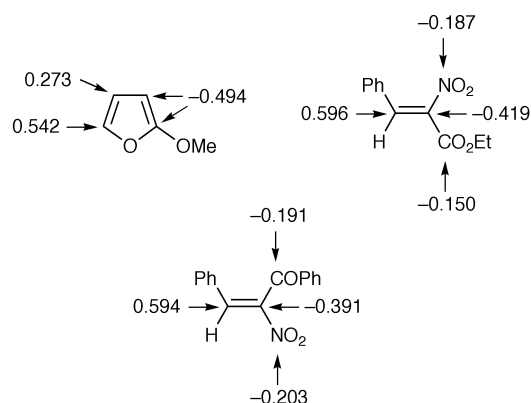
The calculated coefficients of the carbon and nitrogen atoms